Childhood Cancer—Treatment at a Cost

Elaine Ron

Over the last 30 years, more effective treatments, as well as enhanced methods for early diagnosis of cancer have resulted in major improvements in survival for childhood malignancies. The relative 5-year survival rate has risen from 56% for children diagnosed between 1974 and 1976 to 79% for those diagnosed in the period 1995–2001 *(1)*, and the current 10-year survival rate is approximately 75% *(2)*. This increased survival means that the majority of children with cancer can look forward to a long life; however, they may experience multiple late health problems. One of the most alarming long-term consequences of childhood cancer is the occurrence of a second primary malignancy. Although the etiology of many second cancers is unknown, treatment-related cancers are a well-recognized sequela of both radiotherapy and chemotherapy *(3,4)*. An excess risk of subsequent malignancies of the thyroid, breast, bone, soft tissue, and central nervous system (CNS) following radiation treatment for childhood cancer have been reported, whereas secondary leukemia is the main malignancy associated with chemotherapy *(5,6)*.

In this issue of the Journal, Neglia et al. *(7)* report on 116 childhood cancer survivors who developed subsequent malignant and benign tumors of the CNS and 464 childhood cancer survivors, matched on age at initial diagnosis, sex, and time since first diagnosis, who did not develop such subsequent tumors. The study subjects are part of the Childhood Cancer Survivor Study (CCSS), an ongoing multi-institutional retrospective cohort study of over 14 000 5-year cancer survivors who were less than 21 years of age at initial cancer diagnosis. Study participants were diagnosed over a 17-year period (January 1970 to December 1986) and were treated at any of the 26 collaborating centers in the United States or Canada *(6,8)*. The current study is one of a series of evaluations of factors associated with the development of second cancers in this cohort *(6,9–11)*. Data from CCSS investigations have substantially increased our knowledge about health outcomes, behavior and care, as well as quality of life in young cancer patients.

Neglia et al. *(7)* have clearly demonstrated a strong and statistically significant association between radiotherapy and subsequent occurrence of CNS tumors, and in this large study, with detailed organ dose estimates, they also were able to quantify this association. They found strong linear dose–response relationships for all CNS tumors combined and for glioma and meningioma separately. Moreover, they reported that "… radiation therapy was the most important risk factor for the development of a new CNS tumor in survivors of childhood cancers." Radiation-related risks were higher for meningiomas than gliomas, but the radiation effects became apparent earlier for gliomas. Indeed, secondary gliomas rarely occurred more than 15 years after therapeutic radiation for the initial cancer, whereas the largest number of secondary meningiomas appeared after 15 years and the excess risk continued throughout the follow-up period. When radiation dose was taken into account, neither the type of first cancer nor the sex of the subject altered the risk of a subsequent glioma, but being irradiated before age 5 was associated with a higher risk. In contrast, as shown in most other studies of childhood cancer survivors, chemotherapy did not appear to increase the risk of CNS tumors.

Radiobiology has generally held that the carcinogenic effects of radiation decrease at high therapeutic doses due to cell killing *(12)*. Recent research, however, indicates that substantial increased risks of subsequent solid cancers are associated with high therapeutic doses used to treat both adult and childhood cancers *(3–5)*. Neglia et al. *(7)* have shown that radiation doses of 30 Gy or more to the tumor location are associated with statistically significant excesses of benign and malignant CNS tumors. Very few children received doses of 45 Gy or greater, but those who did had a 30-fold statistically significantly higher risk for all CNS tumors combined than survivors who received less than 1 Gy. Sachs and Brenner *(13)* proposed that during radiotherapy the decrease in transformed stem cells due to cell killing would be approximately balanced out by the increase in

Affiliation of author: Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD.

Correspondence to: Elaine Ron, PhD, Radiation Epidemiology Branch, National Cancer Institute, National Institutes of Health, MS7238, 6120 Executive Blvd., Rm. 7054, Bethesda, MD 20892-7238 (e-mail: eron@mail.nih.gov).

DOI: 10.1093/jnci/djj437

transformed cells during organ repopulation, thus the net radiation-related cancer risk would not be expected to decrease rapidly at high doses. In a study also conducted in the CCSS cohort *(10)*, a strong dose-dependent risk of radiation-related thyroid cancer was demonstrated, but the risk began to decrease at thyroid doses above 30 Gy. This apparent difference in results between the two CCSS studies of second cancers might suggest that cells of different organs or tissues may have more or less ability to repopulate.

Findings from the burgeoning second cancer literature should remind us that as new radiotherapy techniques are introduced, consideration should be given to their potential impact on the induction of second cancers. Treating children requires special care because we know from studies of the atomic bomb survivors and other irradiated populations that children have a higher risk of developing radiation-related cancers than adults *(14)*. Intensity-modulated radiotherapy was developed to improve local tumor control and reduce acute toxicity, and it has been used successfully for several cancer types. Some investigators, however, have cautioned that compared with conventional radiotherapy, the widespread use of intensity-modulated radiotherapy could result in a higher incidence of radiation-associated second cancers *(15–17)*.

Although the absolute number of radiation-related CNS tumors is small, the development of a subsequent glioma is particularly devastating because malignant brain tumors are largely fatal. Even benign meningiomas can cause substantial physical and mental limitations depending on their location. The results from this investigation again highlight the need for careful, long-term clinical follow-up of childhood cancer survivors to improve the chances of early diagnosis and successful therapy. Unfortunately, many survivors drop out of medical follow-up fairly soon after their initial cancer diagnosis—20 years later only approximately 40% of a sample of the CCSS cohort reported a cancer-related medical visit *(18,19)*. Oeffinger *(18)* has suggested that some survivors want to think they are cured, whereas others are worried about a recurrence, and avoidance is one way of coping. As data on the lifetime health consequences of successfully treated childhood cancer survivors have become available, the need for more innovative ways to monitor these patients throughout life has become clear.

The rapid increase in survival for childhood cancer has been an important medical success; however, childhood cancer survivors continue to experience late-occurring complications of their disease or therapy. Subsequent new primary cancers are the second most frequent cause of death in the CCSS cohort *(20)*. Thus, it is important to increase our understanding of secondary cancers and what factors affect risk. By identifying persons at high risk of long-term treatment effects, it may be possible to reduce the growing number of patients who develop secondary malignancies by individualizing treatment.

References

(1) Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics. CA Cancer J Clin 2006;56:106–30.

(2) Ries LAG, Harkins D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, et al., editors. SEER cancer statistics review, 1975–2003, based on November 2005 SEER data submission, posted to the SEER web site, 2006. Bethesda (MD): National Cancer Institute. Available at: http://seer.cancer.gov/csr/1975_2003/.

(3) Van Leeuwen FE, Travis LB. Second cancers. In: Devita VT, et al., editors. Cancer: principles and practice of oncology. 7th ed. Philadelphia (PA): Lippincott Williams & Wilkins; 2005. p. 2575–602.

(4) Schottenfeld D, Beebe-Dimmer JL. Multiple cancers. In: Schottenfeld D, Fraumeni JF Jr, editors. Cancer epidemiology and prevention. 3rd ed. New York (NY): Oxford University Press; 2006. p. 1269–80.

(5) Bhatia S, Landier W. Evaluating survivors of pediatric cancer. Cancer J 2005;11:340–54.

(6) Neglia JP, Friedman DL, Yasui Y, Mertens AC, Hammond S, Stovall M, et al. Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 2001;93:618–29.

(7) Neglia JP, Robison LL, Stovall M, Liu Y, Packer RJ, Hammond S, et al. New primary neoplasms of the central nervous system in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 2006;98:1528–37.

(8) Robison LL, Mertens AC, Boice JD, Breslow NE, Donaldson SS, Green DM, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. Med Pediatr Oncol 2002;38:229–39.

(9) Kenney LB, Yasui Y, Inskip PD, Hammond S, Neglia JP, Mertens AC, et al. Breast cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Intern Med 2004;141:590–7.

(10) Sigurdson AJ, Ronckers CM, Mertens AC, Stovall M, Smith SA, Liu Y, et al. Primary thyroid cancer after a first tumour in childhood (the Childhood Cancer Survivor Study): a nested case-control study. Lancet 2005;365:2014–21.

(11) Bassal M, Mertens AC, Taylor L, Neglia JP, Greffe BS, Hammond S, et al. Risk of selected subsequent carcinomas in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. J Clin Oncol 2006;24:476–83.

(12) National Research Council. The effects on populations of exposure to low levels of ionizing radiation: 1980. Washington (DC): National Academy Press; 1980.

(13) Sachs RK, Brenner DJ. Solid tumor risks after high doses of ionizing radiation. Proc Natl Acad Sci U S A 2005;102:13040–5.

(14) National Research Council. Health risks from exposure to low levels of ionizing radiation. BEIR VII. Washington (DC): National Academy Press; 2006.

(15) Hall EJ, Wuu C-S. Radiation-induced second cancers: the impact of 3D-CRT and IMRT. Int J Radiat Oncol Biol Phys 2003;56:83–8.

(16) Hall EJ. Intensity-modulated radiation therapy, protons, and the risk of second cancers. Int J Radiat Oncol Biol Phys2006;65:1–7.

(17) Kry SF, Salehpour M, Followill DS, Stovall M, Kuban DA, White RA, et al. The calculated risk of fatal secondary malignancies from intensity-modulated radiation therapy. Int J Radiat Oncol Biol Phys 2005;62:1195–203.

(18) Oeffinger KC. Longitudinal risk-based health care for adult survivors of childhood cancer. Curr Probl Cancer 2003;27:143–67.

(19) Oeffinger KC, Wallace WHB. Barriers to follow-up care of survivors in the United States and the United Kingdom. Pediatr Blood Cancer 2006;46:135–42.

(20) Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 2002;19:3136–72.